

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

EM

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/20, 9/48, 47/38, 31/66	A1	(11) International Publication Number: WO 99/15155 (43) International Publication Date: 1 April 1999 (01.04.99)
(21) International Application Number: PCT/FI98/00735 (22) International Filing Date: 18 September 1998 (18.09.98) (30) Priority Data: 973733 19 September 1997 (19.09.97) FI (71) Applicant (for all designated States except US): LEIRAS OY [FI/FI]; Pansiontie 45-47, FIN-20210 Turku (FI). (72) Inventors; and (75) Inventors/Applicants (for US only): LEHTOLA, Veli-Matti [FI/FI]; Tapionkatu 22 A 18, FIN-33500 Tampere (FI). RANTALA, Eeva-Maria, Susanne [FI/FI]; Joukahaisentie 17, FIN-21530 Paimio (FI). RANTALA, Pertti, Tapani [FI/FI]; Kierrekujä 3, FIN-20660 Laitinen (FI). (74) Agent: OY JALO ANT-WUORINEN AB; Iso Roobertinkatu 4-6 A, FIN-00120 Helsinki (FI).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: PHARMACEUTICAL PREPARATION COMPRISING CLODRONATE AS ACTIVE INGREDIENT AND SILICIFIED MICROCRYSTALLINE CELLULOSE AS EXCIPIENT (57) Abstract <p>The object of the invention is a pharmaceutical preparation for oral use, especially a tablet, which as its active ingredient contains a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, i.e. a clodronate, especially disodium clodronate, and which as an excipient contains silicified microcrystalline cellulose. Further objects of the invention are a process for the manufacture of said pharmaceutical preparation, and the use of silicified microcrystalline cellulose for the manufacture of said pharmaceutical preparation.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroun	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PHARMACEUTICAL PREPARATION COMPRISING CLODRONATE AS ACTIVE INGREDIENT AND SILICIFIED MICROCRYSTALLINE CELLULOSE AS EXCIPIENT

5 The object of the present invention is a pharmaceutical preparation for oral use, especially a tablet, which as its active ingredient contains a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, i.e. a clodronate, especially disodium clodronate, and which as an excipient contains silicified microcrystalline cellulose. Further objects of the invention are a process for the manufacture of said pharmaceutical preparation, and the use of silicified microcrystalline cellulose for the manufacture of said pharmaceutical preparation.

10

Clodronate or the disodium salt of dichloromethylene bisphosphonic acid, tetrahydrate, is useful for instance in the treatment and prophylaxis of disorders of the calcium metabolism, such as bone resorption, hypercalcaemia and osteoporosis. Based on its ability to form a strong complex with a Ca^{2+} -ion, clodronate removes excessive calcium from the circulation, prevents calcium phosphate from dissolving from the bone and/or acts via cell-mediated mechanisms.

15

Clodronate has previously been administered orally in the form of conventional compressed tablets or capsules. Such a tablet or capsule disintegrates in the stomach of the patient and releases the active agent, which in the acidic environment of the stomach is converted to the free acid form. As clodronic acid is relatively poorly absorbed, the bioavailability of the active agent will be low and consequently clodronate has to be administered in relatively large doses for a prolonged time. A problem with clodronate preparations has therefore been how to achieve a sufficiently high amount and concentration of the active agent in a capsule or tablet, without having to use capsule or tablet sizes which are unpleasantly large for the patient.

25

Another problem with clodronate preparations has been that it is very difficult to mix untreated clodronate raw material to a homogenous mixture with other excipients and active agents present in the preparation. For example EP 275 468 discloses a process wherein clodronate raw material and excipients are mixed dry, a

30

granulating liquid is added, the mixture is wet granulated and the granulate is dried. Due to the properties of clodronate, the clodronate powder thus obtained is, however, inaccurate as regards its composition and obviously difficult to handle (sticky, very poor flow properties). It is thus very difficult in practice to mix it with other substances used in the preparation, as well as to further process it, wherefore, for instance, a relatively large amount of gliding agents is needed. From the homogenous raw powder an unhomogenous and poorly flowing product mass is then obtained, which affects also the accuracy of dosing of the final medicament.

10

The above mentioned problem relating to clodronate raw material has partly been solved by the process described in WO 95/13054, wherein clodronate is crystallized specifically as the disodium clodronate tetrahydrate which is subsequently dry granulated by compressing in such a way that the crystal structure of the disodium clodronate tetrahydrate is preserved. The process is said to lead to ready-to-use granules of uniform quality and good handling characteristics wherefore excipients are needed in considerably smaller amounts than in the previous methods. However, it does not solve the problems relating to the preparation of clodronate dosage forms by wet granulation.

20

Wet granulation is widely used in the pharmaceutical industry in the preparation of solid dosage forms due to the advantages it offers compared to dry granulation and direct compression. Usually the amount of excipients needed in wet granulation is less than that required for direct compression, and thus an acceptably sized tablet may be obtained. Wet granulation also provides the material to be compressed with better wetting properties and the particles comprising the resulting granulate with optimized particle size and shape. Also the amount of drug in the granules is approximately the same, and thus the content uniformity of the final preparation is generally improved.

30

Microcrystalline cellulose is a common excipient used in formulations which are wet granulated prior to tableting. It is suitable not only for adding bulk to the

finished product but also has additional features that facilitate pellet formation. Unfortunately the exposure of microcrystalline cellulose to moisture in the wet granulation process severely reduces the compressibility of this excipient. This is particularly problematic in cases where a pharmaceutical preparation with a high dose of the active agent, such as in the case of clodronate, is desired as the loss of compressibility of the microcrystalline cellulose means that a larger amount of this excipient is needed to obtain an acceptably compressed final product. This in turn adds bulk, making the final product more difficult to swallow and thus reducing patient compliance.

According to the invention it has now been discovered that it is possible to achieve oral dosage forms of clodronate with acceptable size and uniform quality, however, with sufficiently high amount and concentration of the active agent in the preparation. In the preparation process of the novel oral dosage form of clodronate it is possible to use not only dry granulation but also wet granulation and direct compression techniques. This is achieved if the pharmaceutical preparation is an oral dosage form comprising easily compactible silicified microcrystalline cellulose as an excipient.

Silicified microcrystalline cellulose used in the preparation according to the invention is microcrystalline cellulose which has been coprocessed with from about 0.1 to about 20 % silicon dioxide, SiO_2 , based on the amount of microcrystalline cellulose. It is an agglomerate of microcrystalline cellulose and silicon dioxide in which the microcrystalline cellulose and silicon dioxide are in intimate association with each other. This means that the silicon dioxide has been integrated with the microcrystalline cellulose particles but there is no chemical interaction between the two materials. In practice this is achieved e.g. by spray-drying a suspension of microcrystalline cellulose and silicon dioxide.

The advantage of the use of silicified microcrystalline cellulose in clodronate preparations is overall improved functionality in terms of e.g. powder flow, compactibility, tablet strength and especially reduced friability. Solid dosage forms

containing high load of clodronate are now obtainable by direct compression, dry granulation or wet granulation technique. The amount of the silicified microcrystalline cellulose which must be used in the preparation process to obtain an acceptable solid dosage form is substantially reduced, compared to the amount of usual microcrystalline cellulose which must be used for the same purpose. This naturally results in substantial reduction in tablet size. The solid clodronate preparations according to the invention are also of uniform quality and possess excellent disintegration and dissolution properties.

Extensive friability has been a problem especially with tablets containing clodronate. Extensive friability means that tablets are easily crumbled or split into pieces. Surprisingly, this problem can also be overcome by the use of silicified microcrystalline cellulose. A person skilled in the art would expect that the silicon dioxide in the silicified microcrystalline cellulose functions the opposite way when used in clodronate preparations, i.e. that it would decrease crushing strength and increase friability as gliding agents usually do.

However, one of the advantages of the use of silicified microcrystalline cellulose for the manufacture of clodronate preparations is that the silicon dioxide of the silicified microcrystalline cellulose may also function as a gliding agent while it also improves the properties of the microcrystalline cellulose.

In the process of preparing clodronate tablets containing silicified microcrystalline cellulose, it is also possible to first granulate clodronate (either by wet granulation or dry granulation technique) and then to mix the dry granules with silicified microcrystalline cellulose and, if desired, with other excipients before direct compression of the mixture into tablets. This process is technically very feasible and provides clodronate tablets with all the advantages mentioned above.

Further advantages of the use of silicified microcrystalline cellulose for the manufacture of clodronate preparations, especially clodronate tablets, are an increase in the production rate and, consequently, a technically and economically feasible

production process. Tablets containing clodronate and usual microcrystalline cellulose can be formed into tablets only at very low rates compared to tablets containing clodronate and silicified microcrystalline cellulose. The use of silicified microcrystalline cellulose enables the production rates to be increased considerably without adversely affecting the quality of tablets, as is shown in Example 8.

If desired, also other excipients in addition to silicified microcrystalline cellulose may be used in the solid dosage forms according to the invention. These excipients are known to a person skilled in the art, and their use in the manufacture of clodronate preparations has been disclosed e.g. in EP 336 851, US 3,683,080 and US 4,234,645.

Consequently, the preparation according to the invention may further comprise conventional gliding agents and lubricants, such as stearic acid or its salts (Mg-, Ca-), talc, starch, or a mixture of two or more gliding agents. If desired, also additional colloidal silica may be added in addition to what is included in the silicified microcrystalline cellulose.

Filling agents (weight balancing agents) which may be used are for example lactose, starch or its derivatives, mannitol, glucose, saccharose, microcrystalline cellulose, or a mixture of two or more filling agents. Also natural or artificial flavouring and sweetening agents may be used.

If desired, also disintegrants can be added to the preparation. These are disintegrants generally known in the art, such as for example cross-linked sodium carboxymethylcellulose, starch or its derivatives, croscarmellose, crospovidone, or mixtures of two or more disintegrants.

By using certain excipients one can also regulate, if desired, whether a preparation is to decompose in the stomach or only later in the gastrointestinal tract, and also the dissolving rate. Thus the preparation can be coated with as such known film forming agents, which dissolve at the desired pH, such as for example with

shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate or various acryl and methacryl acid derivatives. Film forming agents are known to a person skilled in the art and are commercially available.

5

The composition comprising clodronate and silicified microcrystalline cellulose is suitable for administration not only as a tablet but also as a number of different formulations. Thus it can for example be filled in capsules, or used as granules or a powder according to the methods generally known in the art, and further coated, if desired. Especially preferred are tablets and capsules.

10

The amount of clodronate in the drug delivery form according to the invention can vary within wide limits, e.g. from 10 to 95 % by weight, being typically 50 to 90 % by weight. The amount of silicified microcrystalline cellulose can vary e.g. from about 1 to about 50 % by weight, being typically from about 5 to about 25 % by weight. Preferably the preparation according to the invention comprises 60 to 80 % by weight of anhydrous disodium clodronate, about 8-20 % by weight of silicified microcrystalline cellulose, and 0.5-10 % other excipients such as lubricants and disintegrants.

15

20

The following examples illustrate the invention without limiting the same.

Example 1

25 Tablets were prepared with the following composition per tablet:

	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
	Silicified microcrystalline cellulose	205 mg
30	Carmellose sodium	22 mg
	Stearic acid	15 mg
	Magnesium stearate	8 mg

The silicified microcrystalline cellulose used (Prosolv 90, Mendell, USA) had a 2 % w/w silicon dioxide concentration.

5 In the first stage of the tablet preparation, the dry granulated clodronate was moistened with stearic acid in ethanol and then dried at about 30 °C to a moisture content of appr. 18.5 - 20 %. The dried granules were then sieved through a 1.5 mm sieve. Thereafter the clodronate-stearic acid granules were mixed with car-
10 mellose sodium, silicified microcrystalline cellulose and magnesium stearate. The mixture was formed into tablets in a tableting apparatus, using 9 x 20 mm punches to form tablets of a mean weight of 1177 mg (\pm 2.5 %) and of a suitable strength, for example 4 - 10 kg.

If desired, the prepared tablets may be coated with a coating solution, the composition of which per tablet may be for example the following:

15	Methyl hydroxypropylcellulose phthalate	42.8 mg
	Diethyl phthalate	6.4 mg
	Ethanol	q.s.
	Purified water	q.s.

20

Example 2

Tablets were prepared with the following composition per tablet:

25	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
	Silicified microcrystalline cellulose	155 mg
	Carmellose sodium	22 mg
	Stearic acid	15 mg
30	Magnesium stearate	8 mg

The tablets were prepared essentially as described in Example 1, using the same kind of silicified microcrystalline cellulose as in Example 1.

Example 3

5

Tablets were prepared with the following composition per tablet:

	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
10	Silicified microcrystalline cellulose	155 mg
	Carmellose sodium	22 mg
	Stearic acid	15 mg
	Magnesium stearate	8 mg

15 The silicified microcrystalline cellulose used (Prosolv 50, Mendell, USA) had a 2 % w/w silicon dioxide concentration. The tablets were prepared essentially as described in Example 1.

Example 4

20

Tablets were prepared with the following composition per tablet:

	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
25	Silicified microcrystalline cellulose	140 mg
	Carmellose sodium	22 mg
	Stearic acid	15 mg
	Polyvinylpyrrolidone	15 mg
	Magnesium stearate	8 mg

30

The silicified microcrystalline cellulose used (Prosolv 90, Mendell, USA) had a 2 % w/w silicon dioxide concentration. The tablets were prepared essentially as

described in Example 1, with the exception that stearic acid was dissolved in polyvinylpyrrolidone instead of ethanol.

Example 5

5

Tablets were prepared with the following composition per tablet:

	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
10	Silicified microcrystalline cellulose	125 mg
	Carmellose sodium	22 mg
	Stearic acid	15 mg
	Magnesium stearate	8 mg

- 15 The tablets were prepared essentially as described in Example 1, using the same kind of silicified microcrystalline cellulose as in Example 1.

Example 6

- 20 Tablets were prepared with the following composition per tablet:

	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
	Silicified microcrystalline cellulose	132 mg
25	Carmellose sodium	22 mg
	Stearic acid	15 mg
	Magnesium stearate	8 mg

- 30 The tablets were prepared essentially as described in Example 1, using the same kind of silicified microcrystalline cellulose as in Example 1.

Example 7

Tablets were prepared with the following composition per tablet:

5	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
	Silicified microcrystalline cellulose	165 mg
	Carmellose sodium	22 mg
	Stearic acid	15 mg
10	Magnesium stearate	8 mg

The silicified microcrystalline cellulose used (Prosolv 50, Mendell, USA) had a 2 % w/w silicon dioxide concentration. The tablets were prepared essentially as described in Example 1, using tableting speeds as indicated in Table 1. The results from the measurements of crushing strength and friability are also shown in Table 1.

Table 1. Crushing strength and friability of tablets according to Example 7, prepared at different tableting speeds

20	Tableting speed	Crushing strength	Friability
	30 000 tablets/h	16 kp	0.11 %
	40 000 tablets/h	18 kp	0.20 %

Example 8

Tablets having the same composition as the tablets prepared in Example 6 were prepared at different tableting speeds. For comparison, tablets were also prepared at different tableting speeds with the following composition per tablet:

	Disodium clodronate tetrahydrate 1000 mg responding	
	anhydrous disodium clodronate	800 mg
	Microcrystalline cellulose (Emcocel 50 M)	132 mg
	Carmellose sodium	22 mg
5	Stearic acid	15 mg
	Magnesium stearate	8 mg

Crushing strength and friability of the obtained tablets were measured. The results are shown in Table 2.

10

Table 2. Crushing strength and friability of tablets containing silicified microcrystalline cellulose (A) and of tablets containing usual microcrystalline cellulose (B). Tablets were prepared at different tableting speeds as indicated in Table 2.

15

Tableting speed	Strength of tablets A	Strength of tablets B	Friability of tablets A	Friability of tablets B
15 000 tabl/h	np	13 kp	np	3.0 %
30 000 tabl/h	18 kp	11 kp	0.39 %	38.0 %
50 000 tabl/h	18 kp	*	2.50 %	*

np not performed

* could not be tabletted

20

Tablets containing usual microcrystalline cellulose could not be tabletted using a higher tableting speed than 30 000 tablets/h, because tablets would have broken up.

Claims

1. Pharmaceutical preparation containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid, characterized in that it is an oral solid dosage form comprising silicified microcrystalline cellulose.
2. Preparation according to claim 1, characterized in that it comprises 5-25 % by weight of silicified microcrystalline cellulose.
3. Preparation according to claim 1, characterized in that it comprises
- a) from about 60 to 80 % by weight of anhydrous disodium clodronate;
 - b) from about 8 to 20 % by weight of silicified microcrystalline cellulose; and
 - c) from about 0.5 to 10 % by weight of lubricants and/or disintegrants.
4. Preparation according to any one of the preceding claims wherein silicon dioxide is present in the silicified microcrystalline cellulose in an amount of from about 0.1 to 20 % by weight, based on the weight of the microcrystalline cellulose.
5. Preparation according to any one of the preceding claims, characterized in that it is a tablet or capsule.
6. Preparation according to any one of the preceding claims, characterized in that the salt of dichloromethylene bisphosphonic acid is the disodium salt.
7. Process for the manufacture of a pharmaceutical preparation according to claim 1 characterized in that a wet granulation technique is used.
8. Process for the manufacture of a pharmaceutical preparation according to claim 1, characterized in that a dry granulation technique is used.

9. Process for the manufacture of a pharmaceutical preparation according to claim 1, characterized in that a direct compression technique is used.
10. Use of silicified microcrystalline cellulose for the manufacture of a pharmaceutical preparation containing as an active agent a pharmacologically acceptable salt of dichloromethylene bisphosphonic acid.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/00735

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/20, A61K 9/48, A61K 47/38, A61K 31/66
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9621429 A1 (EDWARD MENDELL CO., INC.), 18 July 1996 (18.07.96)	1-10
	--	
A	WO 9426310 A1 (BOEHRINGER MANNHEIM GMBH), 24 November 1994 (24.11.94)	1-10
	--	
A	WO 9513054 A1 (LEIRAS OY), 18 May 1995 (18.05.95)	1-10
	--	

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

G document member of the same patent family

Date of the actual completion of the international search

22 December 1998

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Date of mailing of the international search report

04-01-1999

Authorized officer

Anneli Jönsson
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT
Information on patent family members

01/12/98

International application No.

PCT/FI 98/00735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9621429 A1	18/07/96	AU 698667 B	05/11/98
		AU 4759896 A	31/07/96
		AU 5019996 A	07/08/96
		BR 9605245 A	16/09/97
		BR 9605329 A	16/09/97
		CA 2183881 A	18/07/96
		CA 2183882 A	25/07/96
		EP 0749300 A	27/12/96
		EP 0752848 A	15/01/97
		FI 963496 A	06/11/96
		FI 963497 A	06/11/96
		HU 9602360 A	28/08/97
		HU 9602361 A	28/08/97
		IL 116674 D	00/00/00
		IL 116675 D	00/00/00
		JP 10500426 T	13/01/98
		NO 963732 A	08/11/96
		NO 963733 A	06/09/96
		US 5585115 A	17/12/96
		US 5725883 A	10/03/98
		US 5725884 A	10/03/98
		US 5741524 A	21/04/98
		WO 9622080 A	25/07/96
WO 9426310 A1	24/11/94	AT 128 U	27/03/95
		AT 128363 T	15/10/95
		AU 687744 B	05/03/98
		AU 4702093 A	12/12/94
		BR 9307859 A	09/01/96
		CA 2162470 A,C	24/11/94
		CN 1095267 A	23/11/94
		CZ 9500100 A	18/10/95
		DE 4322057 A	12/01/95
		DE 59300688 D	00/00/00
		DK 625355 T	27/12/95
		EP 0625355 A,B	23/11/94
		SE 0625355 T3	
		EP 0697890 A	28/02/96
		ES 2065313 T	16/02/95
		FI 945313 A	13/12/94
		GR 3017547 T	31/12/95
		GR 94300095 T	31/01/95
		HU 70214 A	28/09/95
		HU 9403160 D	00/00/00
		JP 8509697 T	15/10/96
		NO 944405 A	24/11/94
		NZ 254765 A	24/02/97
		PL 173026 B	30/01/98
		PL 307133 A	02/05/95
		SK 4895 A	08/01/97
		US 5650168 A	22/07/97
		DE 9307393 U	04/11/93
		ZA 9306041 A	20/02/95

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/12/98

International application No.

PCT/FI 98/00735

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9513054 A1	18/05/95	AU 679586 B	03/07/97
		AU 8108794 A	29/05/95
		CA 2175994 A	18/05/95
		CN 1134664 A	30/10/96
		CZ 9601327 A	16/10/96
		EP 0727983 A	28/08/96
		FI 94926 B,C	15/08/95
		FI 935019 A	13/05/95
		HU 75228 A	28/04/97
		HU 9601257 D	00/00/00
		IL 111596 D	00/00/00
		JP 9504800 T	13/05/97
		NO 961906 A	23/05/96
		NZ 275833 A	24/10/97
		PL 314299 A	02/09/96
		SK 60696 A	05/02/97
		US 5776499 A	07/07/98
		ZA 9408974 A	21/11/95
